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Optimising preterm nutrition: present and future

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The goal of preterm nutrition in achieving growth and body composition approximating that of the fetus of the same postmenstrual age is difficult to achieve. Current nutrition recommendations depend largely on expert opinion, due to lack of evidence, and are primarily birth weight based, with no consideration given to gestational age and/or need for catch-up growth. Assessment of growth is based predominately on anthropometry, which gives insufficient attention to the quality of growth. The present paper provides a review of the current literature on the nutritional management and assessment of growth in preterm infants. It explores several approaches that may be required to optimise nutrient intakes in preterm infants, such as personalising nutritional support, collection of nutrient intake data in real-time, and measurement of body composition. In clinical practice, the response to inappropriate nutrient intakes is delayed as the effects of under- or overnutrition are not immediate, and there is limited nutritional feedback at the cot-side. The accurate and non-invasive measurement of infant body composition, assessed by means of air displacement plethysmography, has been shown to be useful in assessing quality of growth. The development and implementation of personalised, responsive nutritional management of preterm infants, utilising real-time nutrient intake data collection, with ongoing nutritional assessments that include measurement of body composition is required to help meet the individual needs of preterm infants.

Body composition: Nutritional requirements: PEA POD: Preterm infant

The goal of neonatal nutrition in the preterm infant is to achieve postnatal growth and body composition approximating that of a normal fetus of the same postmenstrual age[1], and to obtain a functional outcome comparable with infants born at term[2]. Neonatal units (NU) attempt to achieve this by implementing nutrition policies incorporating growth assessment, but this has its challenges.

Firstly, the exact nutritional requirements of preterm infants (born < 35 weeks completed gestation) are not yet fully known, and current published nutrition recommendations[2–5] are based on limited evidence and depend largely on expert opinion. Thus, there is an ongoing debate as to the validity of these recommendations. In recent years, mounting evidence proposes a more 'aggressive' approach to the nutritional management of preterm infants, with the aim of reducing nutrient deficits and postnatal growth failure[6,7]. However, aggressive nutrition and accelerated growth in infancy have been associated with the development later in life of an increased and aberrant adiposity, which is a marker of morbidity risk[8].

Secondly, the current assessment of growth is predominately based on anthropometry, the measurement of

Abbreviations: AA, amino acids; BW, birth weight; HM, human milk; NU, neonatal units; PN, parenteral nutrition.
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weight, length and head circumference, with insufficient attention given to the quality of growth, in terms of fat mass and fat-free mass. Research to date has informed us that when preterm infants were assessed at term corrected age, they had an altered body composition when compared with term infants[9–11]. Furthermore, changes in an infant's growth pattern[12–14] and body composition[15] in early life may exert programming effects on disease risk in later life. The accurate and non-invasive measurement of body composition has been shown to be useful in assessing quality of growth.

To date, there is insufficient data assessing the adequacy of nutrient intake on growth and subsequent body composition, to provide clear, evidence-based nutrition guidelines for this vulnerable patient group. Studies assessing the adequacy of nutrient intakes after the implementation of nutrition guidelines, still focus on the rate rather than the quality of growth[16,17]. The assessment of the pattern of growth and changes in body composition in early infancy will enhance the knowledge of the nutritional requirements of preterm infants and provide evidence to inform future nutrition recommendations. The present paper provides a review of the current literature on the nutritional management and assessment of growth in preterm infants. It also explores several elements that may be essential for optimising nutrient intakes in preterm infants, such as measurement of body composition, collection of nutrient intake data in real-time and personalising nutritional support.

Nutrient requirements and recommendations

Nutrient requirements of preterm infants have been determined by two methods, the factorial method and the empirical method. The former derived requirements from accretion rates of nutrients derived from the analysis of fetal body composition at different stages of gestation[18]. The empirical method involved the manipulation of nutrient intakes and observation of the growth response, comparing actual energy/protein intakes with actual growth[19].

Several expert groups have formulated international consensus guidelines for the nutritional management of preterm infants (Tables 1 and 2)[2–5] that have allowed NU to introduce and develop nutrition policies to improve standards of nutritional care. The first set of recommendations on nutrition of the preterm infant was published by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition in 1987, and provided guidance on feeding the preterm infant[20]. Published international nutrition guidelines are available in the book *Nutrition of the Preterm Infant: Scientific Basis and Practical Guidelines*, edited by Tsang *et al.*[4]. These recommendations have recently been updated by Koletzko *et al.*[3]. In Europe, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition released guidelines on parenteral nutrition (PN) in 2005[5], but unlike Tsang *et al.*[4], these guidelines give broad recommendations about PN requirements. They provide neither the specific guidance as to what daily prescriptions should be, nor the increment of PN in early postnatal life. In 2010, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition published enteral nutrition guidelines[2], which are consistent with, but not identical to, the recommendations from Tsang *et al.*[4]. These guidelines propose advisable ranges for nutrient intakes for stable-growing preterm infants up to a weight of 1800 g. There are no specific recommendations for infants weighing <1000 g because data are lacking for most nutrients in this group; protein is the exception.

Although much progress has been made in the field of neonatal nutrition over the past few decades, the nutritional requirements of preterm infants are still not yet fully known and there are limitations to the current recommendations[2,4,5]. Firstly, they are based on limited evidence and largely depend on expert opinion. Secondly, they are primarily birth weight (BW) based, and do not account for gestational age. Preterm infants are a heterogeneous population in terms of their nutritional and growth status, with those infants born early likely to have different nutritional needs than those born late, related to their more immature physiological development. Nutrient requirements cannot be consistent throughout gestation; thus, recommendations should take this into consideration. And thirdly, these recommendations are based on the needs for maintenance and growth and do not take into account the need for catch-up growth. The nutrient requirements of preterm infants born early have not been extensively examined, and there are no published studies stratifying infants by both BW and gestational age. More research is required to determine if recommended intakes should consider both gestational age and the need for catch-up growth, and not just BW.

Nutritional management

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition recommends the implementation of multidisciplinary paediatric nutrition support teams in hospitals to screen patients for nutritional risk, identify patients who require nutritional support, and provide adequate nutritional management[21]. It has been shown that implementation of a multidisciplinary team that includes a registered dietitian improves nutritional outcomes of preterm infants in the NU[22]. In particular, involvement of registered dietitians in NU increases the intensity of important aspects of nutritional care[23]. There is substantial evidence to support the role of nutrition guidelines in clinical practice with standardised feeding regimens suggested to be the single most important global tool to prevent necrotising enterocolitis in preterm infants[24]. In addition, improvements in nutrient intakes and growth are observed after the implementation of evidence-based nutrition support practices[16,25,26].

Nutrient intake in preterm infants is divided into parenteral and enteral routes. Preterm infants are initially

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Table 1. Recommendations for parenteral nutrition for preterm infants

	Koletzko *et al.*[5]*	Tsang *et al.*[4]†			
Nutrient	Initial and target doses		Day 1	Days 2–7‡	Growing
Energy (kcal/kg/d)	Target 110–120	ELBW	40–50	75–85	105–115
		VLBW	40–50	60–70	90–100
Amino acids (g/kg/d)	Day 1: ≥1·5	ELBW	2·0	3·5	3·5–4·0
	Maximum 4·0	VLBW	2·0	3·5	3·2–3·8
Lipid (g/kg/d)	Start day 1·0–3·0	ELBW	1·0	1·0–3·0	3·0–4·0
	Target 3·0–4·0	VLBW	1·0	1·0–3·0	3·0–4·0
Carbohydrate (g/kg/d)	Day 1: 5·8–11·5	ELBW	7·0	8·0–15·0	13·0–17·0
	Maximum 18·0	VLBW	7·0	5·0–12·0	9·7–15·0

ELBW, extremely low birth weight infant (<1000 g); VLBW, very low birth weight infant (1000–1500 g).
* Reflects European recommendations.
† Reflects global recommendations.
‡ Days 2–7 indicate the period of metabolic and physiologic instability after birth and may last for up to 7 d.

Table 2. Recommendations for enteral nutrition for preterm Infants

Nutrient	Agostoni *et al.*[2]*	Koletzko *et al.*[3]†	Tsang *et al.*[4]†
Energy (kcal/kg/d)	110–135	110–130	ELBW 130–150 VLBW 110–130
Protein (g/kg/d)	BW < 1000 g: 4·0–4·5 BW 1000–1800 g: 3·5–4·0	3·5–4·5	ELBW 3·8–4·4 VLBW 3·4–4·2
Fat (g/kg/d)	4·8–6·6	4·8–6·6	ELBW 6·2–8·4 VLBW 5·3–7·2
Carbohydrate (g/kg/d)	11·6–13·2	11·6–13·2	ELBW 9·0–20·0 VLBW 7·0–17·0

ELBW, extremely low birth weight infant (<1000 g); VLBW, very low birth weight infant (1000–1500 g); BW, birth weight.
* Reflects European recommendations.
† Reflects global recommendations for infants with a BW up to 1500 g.

dependent on receiving nutrition parenterally due to immaturity of the gastrointestinal tract precluding the digestion and absorption of adequate nutrients, followed by the subsequent slow initiation and advancement of enteral nutrition until full enteral feeds are established.

Evidence base for parenteral nutrition guidelines

Conventional PN consists of an aqueous solution containing glucose, amino acids (AA) and electrolytes (± vitamins and trace elements) and a lipid emulsion (± vitamins) that are infused separately. PN can be prescribed on an individual basis (individualised PN) typically every 24 h, whereby nutrients (± acetate) are individually prescribed specific to each infant's requirements. Alternatively, standardised PN can be used, containing a fixed amount of nutrients that cannot be altered. More recently, some units have started to use concentrated standardised PN (fixed amount of nutrients in a low volume), which prevents nutrient intakes being compromised when fluid is restricted or while enteral feeds are introduced and advanced. It has been shown to be effective in optimising nutrient intakes in the PN-dependent period[27–29], and also has the added advantage of being cheaper than formulating individual solutions[30,31].

A minimum AA supply of 1·5–2 g/kg per d[4,5] on the first day of life should be provided to avoid catabolism, establish anabolism and promote linear growth. AA are generally advanced in a stepwise manner, and a maximum intake of 4 g/kg per d is recommended[4,5]. Protein-to-energy ratios are important, and most authorities suggest 104·6–167·36 kJ (25–40 kcal) of non-protein energy is required per gram AA to promote lean mass accretion[32]. Recently, evidence has supported a more 'aggressive' approach for early AA initiation in preterm infants[6,33], with the initiation of 2–2·5 g/kg per d[34,35] immediately after birth suggested. This more aggressive approach not only prevents catabolism, but may also promote improved growth and neurodevelopmental outcomes[6,7].

Lipids constitute not only an important source of energy due to their high-energy density, but also a source of essential fatty acids and long-chain PUFA. In a recent systematic review and meta-analysis by Vlaardingerbroek *et al.*[36], the initiation of lipids within the first 2 d of life in preterm infants appeared to be safe and well tolerated. More recently, Vlaardingerbroek *et al.*[37] demonstrated that preterm infants tolerated 2–3 g/kg per d lipid administration starting at birth, with no increased incidence of adverse events in the short-term but possible long-term effects remain unknown.

Glucose is the major energy source and the most widely used intravenous carbohydrate for neonates because it is readily available to the brain. Intravenous glucose must commence as soon as possible after birth, with an initial minimum glucose infusion of 4–8 mg/kg per min to prevent

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hypoglycaemia[5]. Maximal glucose oxidation in preterm infants is 8·3 mg/kg per min (12 g/kg per d) after birth[5].

Evidence base for enteral nutrition guidelines

The American Academy of Pediatrics[45] recommends the use of mother's own milk, fresh or frozen, as the first choice in preterm infant feeding, and if mother's own milk is unavailable or is contraindicated, pasteurised donor milk is the recommended alternative. When neither mother's own milk or donor milk is available, preterm formula should be used[38]. There are several significant short- and long-term beneficial effects of feeding preterm infants human milk (HM), including lower incidence of sepsis and necrotising enterocolitis [39–41], improved feeding tolerance, and the faster achievement of full enteral feeds[42,43].

It is generally acknowledged that HM cannot adequately support growth of preterm infants because it does not meet the requirements for many nutrients, most notably protein, calcium and phosphorus, and fortification is therefore required[44,45]. In general, commercially available fortifiers contain protein, carbohydrate and/or fat, electrolytes, vitamins and minerals. Recently, it has been shown that the initiation of fortification with the first feed was well tolerated[46]. The most widely used fortification method involves adding a standard amount of fortifier to HM. However, there is now growing interest in individualising the nutrient fortification of HM to address each preterm infant's unique nutritional requirements and differences in HM composition[47,48]. There are two models of individualisation: targeted fortification[49] and adjustable fortification[50]. The concept of targeted fortification is that the HM is analysed periodically and a target nutrient intake, for instance, protein, is chosen according to the predefined requirements of preterm infants. The amount of fortifier added to reach the target intake is dependent on the protein content of the milk. The adjustable fortification method does not make any assumptions regarding an infant's protein requirements; protein intake is adjusted on the basis of the infant's metabolic response, evaluated through periodic determinations of blood urea nitrogen.

Enteral feeds are generally initiated within 24–72 h after birth. Minimal enteral feeds (<24 ml/kg per d) may be given for the first few days of life to promote gastrointestinal maturation and to reduce mucosal atrophy[51]. A recent systematic review demonstrated that slower feed advancement (<24 ml/kg per d) did not reduce the incidence of necrotising enterocolitis in preterm infants compared with faster rates of 25–35 ml/kg per d[52]. Protocols in vitamin, trace element and mineral supplementation vary considerably amongst NU.

Nutritional concerns arising from current nutritional management

Provision of nutrition in the NU is often overlooked, as the effects of under- or overnutrition are not immediate. In addition, the response to inappropriate nutrient intakes is delayed due to limited nutritional feedback at the cot-side, with more acute issues such as cardiovascular and respiratory justifiably taking precedence.

Implementation of nutrition guidelines is challenging and gaps between nutrition guidelines and clinical practice have been extensively reported[53–57], leading to cumulative nutrient deficits[58–60] and inadequate growth[61–64]. A large discrepancy often exists between prescribed and actual nutrient intakes[54,55,59]. The causes of suboptimal nutrient intakes are multifactorial and partly iatrogenic. Reasons include ineffective PN prescribing practices due to fear of metabolic intolerance of PN constituents, nutritionally suboptimal PN weaning protocols, restricted fluid volumes to minimise morbidities related to fluid overload such as patent ductus arteriosus, evolving neonatal chronic lung disease, and feeding intolerance associated with immaturity, sepsis and necrotising enterocolitis [65]. In addition, most nutritional studies do not analyse the macronutrient content of HM, and published values[66] are used to calculate intakes, leading to possible inaccuracies in the estimation of nutrient intakes arising from the HM component of the total nutrient supply. The analysis of HM should be a prerequisite for future nutritional studies.

More recent observations have revealed adverse effects from the enhanced nutritional management of preterm infants, especially to extremely low BW infants[67,68]. Early and high-dose (4 g/kg per d) AA in the first week of life have been reported to impact negatively on growth and neurodevelopment[68], and increase the incidence of electrolyte disturbances, that is, hypophosphataemia and hypokalaemia[17,67,69,70]. This is possibly due to high AA intakes inducing a progressive depletion of phosphate and potassium from accelerated protein synthesis[71]. These findings emphasise the need to undertake preliminary analysis and testing of novel nutritional strategies to optimise nutrient intakes in preterm infants prior to their implementation in intervention studies, due to the risk of unintended adverse effects. Furthermore, real-time nutrient data collection in the NU could play an important role in allowing nutrient deficits or excesses to be promptly identified and responded to in real-time, at the cot-side, to avoid these undesirable effects. The focus of future research should be to develop a software tool that will collect real-time nutritional data at the cot-side to enable the assessment and monitoring of nutrient intakes in preterm infants.

Assessment of growth

It is clear that the goal of nutritional management of preterm infants should be to optimise quantitative and qualitative rates of growth to limit long-term morbidity and enhance long-term outcomes. The adequacy of nutrient intakes among infants is currently monitored by changes in weight gain, length and head circumference. Serial measurements of length and head circumference are important as they are better indicators of true growth, rather than weight alone, which may fluctuate

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due to changes in fluid balance rather than adipose or lean tissue mass. Whilst these measurements provide an important tool for assessing growth of infants, they do not provide information on the quality of growth achieved. The accurate and non-invasive measurement of infant body composition has been shown to be useful in assessing the quality of growth. Over the past two decades, the applicability of air displacement plethysmography for the assessment of human body composition has been developed[72,73], and is now the preferred method for paediatric measurements[74].

Anthropometry

Weight

The infant should be weighed nude, preferably at the same time of day, on a regularly calibrated electronic scale which is recorded to the nearest 10 g. Weight may need to be measured daily to assist fluid and electrolyte management, and to provide an index to daily growth. Measurements should be plotted weekly on an appropriate growth chart. After birth, contraction of the extracellular fluid results in postnatal weight loss reported to be between 7 and 20 % of BW during the first 3–5 d[6,75]. This weight loss can be further contributed to by catabolism of endogenous glycogen, fat stores and lean tissue if adequate nutrition is not provided. The smallest infants tend to have the largest loss related to their higher body water composition and thinner epidermis. BW should be regained by 14–21 d of life[62,76,77]. More recent studies evaluating the impact of optimisation of early postnatal nutrition in very low BW infants have demonstrated that BW can be regained as early as 7 d (*n* 102)[16] and 12 d (*n* 123)[25]. It has been proposed that the earlier recovery from initial weight loss during the first days of life appears to be key for optimising growth in extremely preterm infants, as later catch-up requires a higher growth rate that would be difficult to achieve in most infants[25].

Length

Length measurement compared with weight measurement more accurately reflects lean tissue mass accretion, and is not influenced by fluid status and is therefore, a better indicator of long-term growth. Length should be monitored weekly and plotted on an appropriate growth chart. Accurate length measurements require two examiners, one holding the infant's head, and the other holding the infant's legs, and the average of two measurements taken. To obtain the measurement, the infant should be placed on a flat surface in a supine, fully extended position with knees straightened, and feet at right angles to the body. Plastic, recumbent length boards, for instance, the Leicester Incubator Measure (Harlow, UK) allows body length to be measured in the incubator, to the nearest 1 mm, thereby increasing the accuracy of measurements compared with the use of a measuring tape. An incremental gain in crown to heel length of approximately 0·9–1·1 cm/week should be expected[62,78].

Head circumference

Head circumference is measured to the nearest 1 mm with a non-stretch measuring tape at the maximal occipitofrontal circumference. Head circumference should be measured weekly, and the average of two measurements taken, and plotted on an appropriate growth chart. More frequent measurements may be indicated for infants with micro- or macrocephaly or suspected abnormal increases in head circumference. Head growth may remain normal despite inadequate postnatal nutrition[62]. During the first postnatal week, head circumference may decrease by about 0·5 cm due to extracellular fluid space contraction. A growth rate of approximately 0·9 cm/week is the goal for head circumference[62].

Growth charts

Anthropometric measurements should be plotted on an appropriate growth chart. They provide the basis for growth and nutritional assessment of infants by presenting a comparison of an infant's actual size and growth trajectory with reference data. In the absence of a prescriptive growth chart depicting the growth of preterm infants under optimal conditions, monitoring postnatal growth of preterm infants is complicated, and there is a lack of global consensus on what is the most appropriate growth reference to use. BW growth charts are the mainstay for monitoring growth in preterm infants[79], and they include the WHO[80] and UK-WHO growth chart[81], the CDC (Centers for disease control and prevention) growth chart[82], and more recently, the Fenton growth chart[83]. Establishing a consensus regarding the most appropriate growth reference to use would be an important component in the standardisation of care for preterm infants, and would allow comparisons to be made between institutions and studies.

Body composition measurement

Quality of growth can be assessed by measuring an infant's body composition, which is calculated from body density (body density = body mass/body volume). The air displacement plethysmography methodology is used to obtain a measurement of the infant's body volume, which is used with body weight to determine total body density. This, in turn, is used with the basic two-compartment model of fat mass and fat-free mass to calculate the body's percentage of fat. This technique uses commercial equipment such as a device called the PEA POD (COSMED USA, Inc., Concord, CA, USA) (Fig. 1), which has been validated for use in infants 1000–8000 g[84–86]. The description and operation of the PEA POD are reported elsewhere[84,85]. The PEA POD is a portable device that can be used at the infant's bed side. The test chamber is temperature-controlled and a complete analysis takes about 5 min. Validation of the PEA POD has been performed against the deuterium dilution method and a reference four-compartment model for the estimation of infant body composition[84]. It was found to be accurate and precise, with excellent within-day and between-day reliability[84].

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Fig. 1. PEA POD with an infant in the test chamber and an operator observing the infant's behaviour and the progress of the measurement on the display monitor. (Photograph courtesy of COSMED USA Inc., reproduced with permission.)

Conclusion

To ensure optimal growth and body composition is achieved in preterm infants, their nutritional management should be personalised to meet their individual needs according to their gestational age, BW and their need for catch-up growth. The development and implementation of responsive, personalised nutritional support in preterm infants is required. This should utilise real-time nutrient intake data collection, with ongoing nutritional assessments that includes the measurement of body composition.

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